Relation of Adult-Onset Asthma to Coronary Heart Disease and Stroke

Stephen J. Onufrak, PhD[a,b,*], Jerome L. Abramson, PhD[b], Harland D. Austin, DSc[b], Fernando Holguin, MD, MPH[c], William M. McClellan, MD, MPH[b], and L. Viola Vaccarino, MD, PhD[b,d]

Asthma was associated with atherosclerotic disease in several studies, with evidence that this association may be limited to women. However, most previous studies failed to account for the heterogeneity of asthma subtypes. We previously reported increased carotid intima-medial thickness in women with adult-onset asthma. In this study, the association of adult- and child-onset asthma with incident coronary heart disease (CHD) and stroke were examined. Subjects were classified according to self-report of physician-diagnosed asthma and age of asthma onset. Cox proportional hazards models were used to test the association of adult- and child-onset asthma with incident CHD and stroke, testing for gender interaction. Subanalysis was also performed using only never smokers. Women with adult-onset asthma experienced a 2-fold increase in incident CHD and stroke that was independent of other risk factors, including smoking, body mass index, and physical activity, and persisted when analysis was restricted to never smokers. No significant association was found in women with child-onset asthma or in men. In conclusion, adult-onset asthma may be a significant risk factor for CHD and stroke in women, but not men. **(Am J Cardiol 2008;101:1247–1252)**

Asthma was associated with vascular disease, carotid atherosclerosis, coronary heart disease (CHD), or stroke in at least 9 studies.[1–9] In studies that presented results stratified by gender, there was a suggestion that the association may be stronger for or entirely limited to women.[1–4] However, asthma is not a single disease, but a collection of distinct underlying subtypes with differing causes.[10,11] Child- and adult-onset asthma differ in regard to asthma triggers,[11] gender distribution,[11] and systemic inflammation.[12] We previously reported an association between carotid intima-medial thickness and adult-onset asthma in women in the Atherosclerosis Risk In Communities (ARIC) Study.[4] This association was not observed in women with child-onset asthma or men with either adult- or child-onset asthma. In this study, we examined the association of asthma age of onset phenotypes with incidence of CHD and stroke according to gender within the ARIC cohort.

Methods

Study population: The ARIC Study is a prospective study of the cause of atherosclerotic, cardiovascular, and cerebrovascular disease in 4 US communities in North Carolina, Mississippi, Minnesota, and Maryland.[13] The study population of 15,792 men and women aged 45 to 64 years included both black and white subjects. Subjects completed a baseline clinic visit in 1987 to 1989 and were followed up for incidence of CHD and stroke events. We used publicly available data with follow-up available through 2001 for 15,732 subjects. We excluded subjects missing data for asthma status (n = 28) or who reported ever having asthma but did not report a physician diagnosis of asthma (n = 131). We also excluded subjects with self-reported history of stroke (n = 320) or prevalent CHD (n = 692), defined as history of myocardial infarction (MI), silent MI, or revascularization surgery at baseline. This left 14,567 subjects for analysis.

Baseline assessment of asthma status and other covariates: Based on self-report of physician-diagnosed asthma and age of asthma onset, subjects were classified as having adult-onset asthma if age of onset was ≥21 years or child-onset asthma if onset was at age <21 years. Smoking was measured using self-reported smoking status (former, current, or never). Classification of diabetes was based on ≥1 of fasting plasma glucose >126 mg/dl, nonfasting plasma glucose >200 mg/dl, self-reported diabetes, or use of diabetes medications. Low- and high-density lipoprotein cholesterol were included in models as continuous variables. All laboratory tests were run at centralized chemical, hemostasis, and lipid laboratories, and hematologic tests were run at local laboratories. Hypertension was defined as diastolic blood pressure ≥90 mm Hg, systolic blood pressure >140 mm Hg, or self-report of antihypertensive drug use.[14] Physical activity was assessed according to the scale of Baecke et al,[15] based on frequency, duration, and intensity of physical activity. Education level was classified according to number of years of school completed (<12, 12 to 16, or >16 years). Asthma medication use (β-adrenergic

[a]Agricultural Research Service, US Department of Agriculture, Stoneville, Mississippi; [b]Department of Epidemiology, Rollins School of Public Health, Emory University; [c]Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, and [d]Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia. Manuscript received November 16, 2007; revised manuscript received and accepted December 19, 2007.

This work was supported by Grant No. K24 HL077506 from the National Institutes of Health, Bethesda, Maryland. Dr. Onufrak was supported by a predoctoral fellowship from the American Heart Association, Dallas, Texas (Award Number: 0615219B).

*Corresponding author: Tel: 662-686-3437; fax: 662-686-3522.

E-mail address: steve.onufrak@ars.usda.gov (S.J. Onufrak).

0002-9149/08/$ – see front matter
doi:10.1016/j.amjcard.2007.12.024

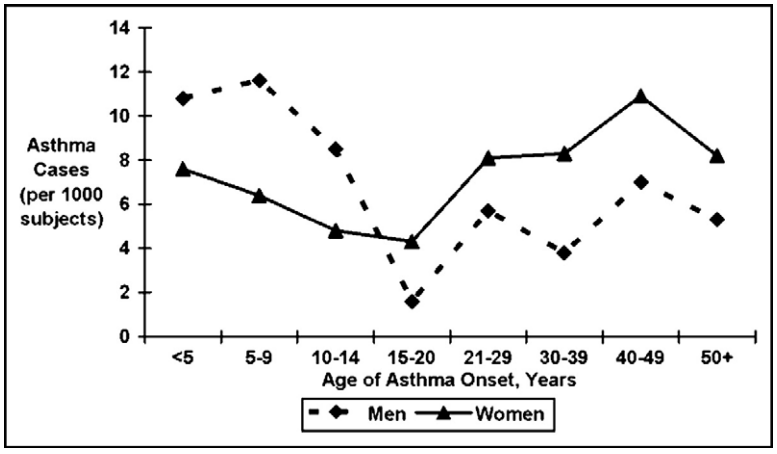

Figure 1. Self-reported age of asthma onset in men and women.

and oral glucocorticoid medication) was classified according to use during the 2-week period before the baseline clinic visit and ascertained by having subjects bring all prescription and nonprescription medications used during this period to the clinic during their baseline visit. Forced expiratory volume in 1 second (FEV_1) and forced expiratory vital capacity were assessed using spirometry according to the ARIC Study protocol.[16] This protocol includes strict quality-control procedures to ensure recorded spirometry measurements are technically acceptable and reproducible.[16] FEV_1 was categorized for use in multivariable analysis according to gender-specific quartiles. Chronic bronchitis and emphysema were classified based on self-report of physician diagnosis.

Ascertainment of incident CHD and stroke events: For our primary analysis, incident CHD was defined as definite or probable MI or fatal CHD. We also performed subanalyses in which incident CHD events included revascularization procedures and silent MI detected using electrocardiography. Incident strokes included both ischemic and hemorrhagic strokes. Potential CHD and stroke events were identified in cohort members through annual follow-up, survey of area hospital discharge lists, and state vital statistics. When discharge summaries indicated diagnosis codes for cardiovascular disease, diabetes, or stroke or included stroke-related keywords, hospital records were abstracted by trained study personnel. Out-of-hospital deaths were investigated using death certificates, interview with $\geq$1 next of kin, and a physician questionnaire, coroner report, or autopsy report. MI events were classified based on chest pain, cardiac enzymes, and electrocardiogram results. Fatal CHD classification was based on chest pain symptoms, cause of death from the death certificate, and available hospital information and medical history, including ARIC clinic visits. For stroke events, records were reviewed in detail by a member of the ARIC Study Stroke-Mortality and Morbidity Classification Committee, and the patient was classified according to type of stroke (ischemic or hemorrhagic). The outcome ascertainment process was described in further detail by ARIC investigators.[17]

Analysis: Analysis was completed using SAS, version 9 (SAS Institute, Cary, North Carolina). Baseline covariates were compared by asthma history in men and women separately using chi-square test, Fisher's exact test, and pooled or unpooled *t* test. Missing covariate values, which occurred at $<$3% for any covariate, were imputed using multiple imputation methods.[18] Crude incidence density rates of CHD and stroke were calculated in men and women for those without asthma, those with child-onset asthma, and those with adult-onset asthma. Crude and multivariate hazard ratios (HRs) comparing patients with each asthma subtype with those without asthma were computed using Cox proportional hazards models. Multivariate models were adjusted for age, body mass index, black race, smoking status, diabetes, hypertension, education level, low- and high-density lipoprotein, and leisure physical activity. We tested for interactions between asthma and gender in crude and multivariate models using Wald's chi-square tests. In subanalyses, we used an expanded definition of CHD to include revascularization and silent MI.

We also performed additional analyses to investigate the impact of asthma medications, lung function, and the respiratory co-morbidities chronic bronchitis and emphysema on the association of asthma with cardiovascular outcomes. To further examine the possible confounding effect of smoking and the possible misclassification of chronic obstructive pulmonary disease (COPD) as asthma on our results, we repeated the analysis in the subgroup of patients who never smoked. Finally, we also performed age-adjusted analysis of women free of diabetes, hypertension, emphysema, and chronic bronchitis. In all these additional analyses, we used a combined outcome of incident CHD or stroke to maximize the number of events in the model.

Results

The distribution of asthma age of onset in men and women is shown in Figure 1. The prevalence of child-onset asthma was higher in men (3.3%) than women (2.5%), whereas adult-onset asthma was more common in women (3.4%) compared with men (2.0%). Compared with their counterparts without asthma, men and women with adult-onset asthma were older and had a higher prevalence of diabetes and hypertension, more pack-years of smoking, higher fibrinogen, and higher prevalence of β-adrenergic and glucocorti-

Table 1
Baseline comparison of men and women according to self-reported asthma history

Variable	Men			Women		
	No Asthma (n = 5,931)	Child-Onset* Asthma (n = 210)	Adult-Onset* Asthma (n = 131)	No Asthma (n = 7,809)	Child-Onset* Asthma (n = 203)	Adult-Onset* Asthma (n = 283)
Age (yrs)	54.3	53.3†	55.4†	53.7	52.9†	54.3
Black race (%)	23.3%	19.1%	15.3%†	29.6%	30.1%	33.2%
High school graduate (%)	77.5%	82.3%	65.7%†	77.2%	76.4%	69.3%†
Body mass index (kg/m^2)	27.4	27.2	27.3	27.8	28.3	28.9†
Diabetes mellitus (%)	10.5%	10.6%	14.5%	10.8%	17.2%†	17.8%†
Hypertension (%)	32.4%	29.2%	37.4%	34.1%	33.0%	43.6%†
Chronic bronchitis (%)	4.0%	15.1%†	27.9%†	9.2%	39.6%†	43.1%†
Emphysema (%)	1.9%	4.3%†	8.4%†	0.9%	3.9%†	5.3%†
Current smoker (%)	27.6%	22.4%	21.4%	24.6%	22.8%	29.0%
Pack-years	21.7	20.1	24.3	10.0	11.2	13.8†
Leisure physical activity index	2.34	2.35	2.35	2.38	2.33	2.29†
FEV_1 (L)	3.37	3.11†	2.74†	2.44	2.20†	2.05†
FEV_1 (% predicted)	91.4%	83.2%†	74.6%†	97.1%	86.5%†	83.3%†
FEV_1/forced expiratory vital capacity	73.5	68.3†	63.5†	75.9	71.1†	70.3†
Low-density lipoprotein cholesterol (mg/dl)	139	135	139	136	133	134
High-density lipoprotein cholesterol (mg/dl)	45	45	47†	58	58	58
Albumin (mg/dl)	3.92	3.96	3.91	3.83	3.78†	3.81
Fibrinogen (mg/dl)	295	294	306	307	315	316†
Present hormone replacement therapy (%)	—	—	—	19.2%	22.6%	15.7%
Postmenopausal or hysterectomy (%)	—	—	—	67.1%	58.9%†	75.9%†
β-Adrenergic asthma medication use (%)	0.6%	6.2%†	29.0%†	0.4%	13.3%†	22.6%†
Oral glucocorticoid asthma medication use (%)	0.5%	2.9%†	12.2%†	1.0%	3.5%†	9.2%†

* Child onset = age <21 years; adult onset = age ≥21 years.
† $p < 0.05$ comparing subjects within asthma subtype with subjects reporting no history of asthma within each gender.

Table 2
Incident coronary heart disease rates and hazard ratios in men and women according to asthma history

	Men			Women		
	No History of Asthma	Child-Onset Asthma	Adult-Onset Asthma	No History of Asthma	Child-Onset Asthma	Adult-Onset Asthma
Crude rate* (cases/person-yrs)	7.85 (565/72,006)	8.52 (22/2,582)	6.22 (10/1,607)	3.52 (348/98,963)	3.49 (9/2,580)	7.34 (25/3,407)
Crude HR (95% CI)	1.0 (reference)	1.08 (0.71–1.66)	0.80 (0.43–1.49)	1.0 (reference)	0.99 (0.51–1.93)	2.10 (1.40–3.16)
Multivariate-adjusted† HR (95% CI)	1.0 (reference)	1.25 (0.82–1.92)	0.71 (0.38–1.32)	1.0 (reference)	0.95 (0.49–1.83)	1.78 (1.18–2.67)

* Per 1,000 person-years.
† Adjusted for age, body mass index, black race, diabetes mellitus, hypertension, education level, low- and high-density lipoprotein cholesterol, and physical activity.

coid steroid asthma medication use at baseline (Table 1). Women with adult-onset asthma also had significantly higher body mass index and lower physical activity and were more often postmenopausal than women without a history of asthma. Compared with patients without asthma, FEV_1, percent of expected FEV_1, and FEV_1/forced expiratory vital capacity were lower in men and women with either asthma subtype, but were lowest in those with adult-onset asthma. Likewise, chronic bronchitis, emphysema, and use of asthma medications were more prevalent in all patients with asthma, but were most prevalent in those with adult-onset asthma (Table 1).

Women, but not men, with adult-onset asthma experienced a 2-fold increase in rate of CHD compared with their counterparts without asthma (Table 2). This association was attenuated, but remained significant, after adjustment for age, body mass index, black race, smoking status, diabetes, hypertension, education level, low- and high-density lipoprotein cholesterol, and physical activity (Table 2). Child-onset asthma was not significantly associated with incident CHD in women or men. Tests of interaction between gender and adult-onset asthma were significant ($p < 0.05$) in all CHD models, whereas interaction tests of child-onset asthma with gender were not. Results were similar in subanalyses in which incident CHD also included revascularization procedures and silent MI, with an adjusted HR of 1.86 (95% confidence interval [CI] 1.31 to 2.63) for women with adult-onset asthma and nonsignificant associations observed in all other asthma–gender subgroups.

Similar to results for CHD, adult-onset asthma was associated with incident stroke in women, but not men, with a

Table 3
Incident stroke rates and hazard ratios in men and women according to asthma history

	Men			Women		
	No History of Asthma	Child-Onset Asthma	Adult-Onset Asthma	No History of Asthma	Child-Onset Asthma	Adult-Onset Asthma
Crude rate* (cases/person-yrs)	3.50 (257/73,489)	2.27 (6/2,639)	1.22 (2/1,634)	2.39 (238/99,443)	3.51 (9/2,565)	5.57 (19/3,411)
Crude HR (95% CI)	1.0 (reference)	0.65 (0.29–1.45)	0.35 (0.09–1.41)	1.0 (reference)	1.47 (0.76–2.87)	2.36 (1.48–3.76)
Multivariate-adjusted† HR (95% CI)	1.0 (reference)	—	—	1.0 (reference)	1.25 (0.64–2.44)	2.08 (1.30–3.32)

* Per 1,000 person-years.
† Adjusted for age, body mass index, black race, diabetes mellitus, hypertension, education level, low- and high-density lipoprotein cholesterol, and physical activity.

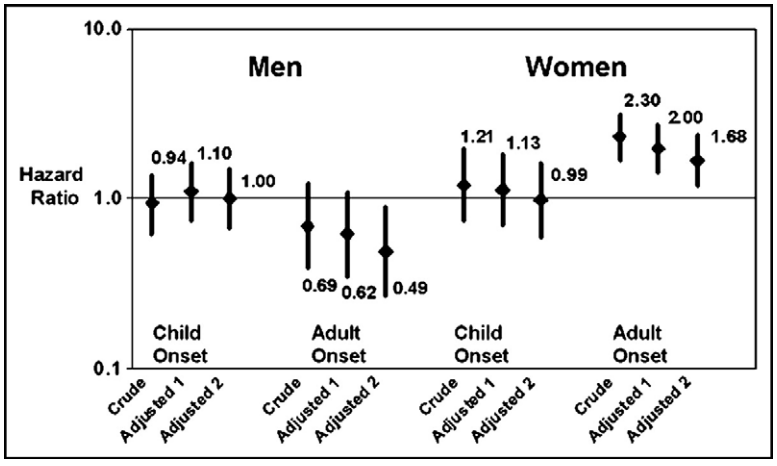

Figure 2. HRs for incident CHD or stroke according to age of asthma onset and gender. Adjusted model 1 includes age, body mass index, black race, smoking status, diabetes mellitus, hypertension, education level, low- and high-density lipoprotein cholesterol, and physical activity; Adjusted model 2 includes model 1 covariates plus FEV_1, chronic bronchitis, emphysema, and use of glucocorticoid or β-adrenergic medicines.

significant gender interaction ($p < 0.05$; Table 3). The association of adult-onset asthma with stroke in women remained significant after adjustment for demographic variables and established CHD risk factors (Table 3). The small numbers of stroke events precluded multivariate analysis in men. Child-onset asthma was not significantly associated with incident stroke in men or women, and the interaction of child-onset asthma and gender was nonsignificant (Table 3).

Because of the similarity of results for CHD and stroke outcomes, we performed additional analyses using a combined end point of incident cardiovascular disease, including CHD or stroke (Figure 2). In the fully adjusted model including covariates for asthma medications, FEV_1, chronic bronchitis, and emphysema, adult-onset asthma was significantly associated with this combined outcome in women (HR 1.68, 95% CI 1.21 to 2.35). Results remained robust in analyses restricted to never smokers, which again confirmed a significant association of adult-onset asthma in women, but not in men or in women or men with child-onset asthma (Table 4). Finally, in age-adjusted analysis in women free of diabetes, hypertension, emphysema, and chronic bronchitis, adult-onset asthma was strongly associated with incidence of CHD or stroke (HR 3.93, 95% CI 2.01 to 7.02), whereas child-onset asthma was not significantly associated (HR 1.80, 95% CI 0.67 to 4.87).

Discussion

In this large community-based follow-up study, women with adult-onset asthma experienced a nearly 2-fold increase in rate of CHD and stroke independent of other risk factors, including smoking, body mass index, and physical activity, that persisted when analysis was restricted to never smokers. This result was consistent with our previous finding that women, but not men, with adult-onset asthma had increased carotid intima-medial thickness compared with their counterparts without asthma[4] and with other reports suggesting a role of asthma in atherosclerotic disease in women, but not men.[1–3]

This was the first study to test the association of asthma age-of-onset subtypes with cardiovascular outcomes. It is recognized that "asthma" is not a uniform disease, but rather a constellation of distinct conditions.[10,11,19] Adult-onset asthma differs from child-onset asthma in several aspects, including its distribution in men and women[11] and its immunologic and inflammatory pathophysiologic characteristics.[10,19] Nevertheless, previous studies of patients with asthma and atherosclerotic outcomes generally ignored asthma subtypes. Three previous studies presented gender-specific results for the association between asthma and CHD. Toren and Lindholm[1] reported age-adjusted standard-

Table 4
Never smokers only: combined coronary heart disease or stroke event rates and hazard ratios in men and women according to asthma history

	Men			Women		
	No History of Asthma	Child-Onset Asthma	Adult-Onset Asthma	No History of Asthma	Child-Onset Asthma	Adult-Onset Asthma
Crude rate* (cases/ person-yrs)	8.31 (181/21,757)	5.49 (5/910)	10.69 (5/468)	4.75 (251/52,868)	5.40 (7/1,296)	10.59 (18/1,699)
Crude HR (95% CI)	1.0 (reference)	0.65 (0.27–1.68)	1.31 (0.54–3.18)	1.0 (reference)	1.14 (0.51–2.43)	2.24 (1.39–3.62)
Multivariate-adjusted† HR (95% CI)	1.0 (reference)	0.74 (0.30–1.80)	1.04 (0.43–2.53)	1.0 (reference)	1.10 (0.52–2.33)	2.05 (1.28–3.31)

* Per 1,000 person-years.
† Adjusted for age, body mass index, black race, diabetes mellitus, hypertension, education level, low- and high-density lipoprotein cholesterol, and physical activity.

ized mortality ratios for ischemic heart disease of 1.4 (95% CI 0.8 to 2.0) in men with asthma and 2.5 (95% CI 1.7 to 3.3) in women with asthma. In a retrospective cohort study of a large insurance cohort, Iribarren et al[2] reported multivariate adjusted HRs of 1.22 (95% CI 1.14 to 1.31) in women with asthma and 0.99 (95% CI 0.93 to 1.05) in men with asthma. Similarly, an earlier report from the ARIC Study found increased risk of stroke in women with asthma, but not men, compared with subjects without asthma, although no association was found with CHD outcomes in either women or men.[3] None of these previous reports distinguished among asthma subtypes. Thus, the lack of association of asthma with CHD reported in the previous ARIC Study probably reflected mixing of the heterogeneous effects of adult- and child-onset asthma subtypes.[3] By separating asthma subtypes, we uncovered an important risk associated with adult-onset asthma in women.

The precise mechanisms underlying the association between adult-onset asthma and atherosclerotic vascular disease in women are unclear. Asthma may predispose to atherosclerosis through specific pathophysiologic pathways, perhaps linked to the chronic inflammatory response of this disorder. Alternatively, the association between asthma and atherosclerosis may be caused by an inherent joint susceptibility to both diseases through shared inflammatory pathways. For example, cysteinyl leukotrienes, potent inflammatory mediators, were implicated in the pathogenesis of both asthma[20] and atherosclerosis.[21] Why is the association between asthma and cardiovascular disease observed in only women with adult-onset asthma? Estrogen, which increases at puberty, modulates the release of proinflammatory cytokines from activated monocytes, macrophages,[22] and vascular cells[23,24] and also regulates the production of leukotrienes from mast cells.[25] The incidence rate of asthma in women is temporally associated with shifts in estrogen levels, with incidence increasing after puberty[26] and peaking during the onset of menopause[27] (Figure 1). Thus, we may speculate that women who develop asthma during these hormonal life events may be particularly susceptible to estrogen-modulated alterations in inflammatory cytokine and leukotriene regulation.

Our study has several strengths. Foremost, the ARIC cohort is large, multiracial, and prospective and includes rich and high-quality subject data. We were able to control for potentially important confounding variables, such as smoking, physical activity, and asthma medication use, and we further addressed confounding by smoking and other factors by performing subanalyses restricted to never-smoking subjects and subjects free of diabetes, hypertension, emphysema, and chronic bronchitis. The major weakness of our study was that asthma status was based on self-report of physician diagnosis. Although there was evidence to suggest that self-reported asthma yielded high specificity,[28] there were also reports to suggest that misdiagnosis of COPD as asthma occurred frequently, and more so in women.[29] Because approximately 85% of patients with COPD had a history of smoking, the persistence of the association of adult-onset asthma with CHD in never-smoking women suggested that the observed association was not likely to be caused by misdiagnosed COPD. Nonetheless, there is the need for further research in which asthma classification is objectively determined through established clinical guidelines. Furthermore, we did not have information for immunoglobulin E levels, asthma triggers, or presence of allergies to differentiate asthma according to allergic status. Other limitations included small numbers of events, particularly stroke, in men with adult-onset asthma and lack of data for such inflammatory markers as C-reactive protein. Finally, because our study was observational, we cannot exclude the influence of unmeasured confounding factors or residual confounding because asthma was associated with many known cardiovascular risk factors.

Acknowledgment: The authors thank the ARIC researchers for their outstanding work and contributions to the study of cardiovascular disease and Sean Coady, MA, for help in data acquisition. The ARIC Study was conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the ARIC Study Investigators. This report was prepared using a limited-access data set obtained by the NHLBI and does not necessarily reflect the opinions or views of the ARIC Study group or the NHLBI. Primary work for this study was performed while Dr. Onufrak was a doctoral student at Emory University, Atlanta, Georgia.

1. Toren K, Lindholm NB. Do patients with severe asthma run an increased risk from ischaemic heart disease? *Int J Epidemiol* 1996;25: 617–620.
2. Iribarren C, Tolstykh IV, Eisner MD. Are patients with asthma at increased risk of coronary heart disease? *Int J Epidemiol* 2004;33:743–748.

3. Schanen JG, Iribarren C, Shahar E, Punjabi NM, Rich SS, Sorlie PD, Folsom AR. Asthma and incident cardiovascular disease: the Atherosclerosis Risk in Communities Study. *Thorax* 2005;60:633–638.
4. Onufrak S, Abramson J, Vaccarino V. Adult-onset asthma is associated with increased carotid atherosclerosis among women in the Atherosclerosis Risk in Communities (ARIC) Study. *Atherosclerosis* 2007;195:129–137.
5. Zureik M, Kony S, Neukirch C, Courbon D, Leynaert B, Vervloet D, Ducimetiere P, Neukirch F. Bronchial hyperresponsiveness to methacholine is associated with increased common carotid intima-media thickness in men. *Arterioscler Thromb Vasc Biol* 2004;24:1098–1103.
6. Liss GM, Tarlo SM, Banks D, Yeung KS, Schweigert M. Preliminary report of mortality among workers compensated for work-related asthma. *Am J Ind Med* 1999;35:465–471.
7. Liss GM, Tarlo SM, Macfarlane Y, Yeung KS. Hospitalization among workers compensated for occupational asthma. *Am J Respir Crit Care Med* 2000;162:112–118.
8. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005;128:2099–2107.
9. Knoflach M, Kiechl S, Mayr A, Willeit J, Poewe W, Wick G. Allergic rhinitis, asthma, and atherosclerosis in the Bruneck and ARMY studies. *Arch Intern Med* 2005;165:2521–2526.
10. Bel EH. Clinical phenotypes of asthma. *Curr Opin Pulm Med* 2004; 10:44–50.
11. Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet* 2006;368:804–813.
12. Olafsdottir IS, Gislason T, Thjodleifsson B, Olafsson I, Gislason D, Jogi R, Janson C. C Reactive protein levels are increased in nonallergic but not allergic asthma: a multicentre epidemiological study. *Thorax* 2005;60:451–454.
13. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol* 1989;129:687–702.
14. Jones DW, Hall JE. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and evidence from new hypertension trials. *Hypertension* 2004;43:1–3.
15. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* 1982;36:936–942.
16. The ARIC Investigators. ARIC Protocol 4. Pulmonary Function Assessment, Version 7. Chapel Hill, NC: National Heart Lung and Blood Institute, National Institutes of Health, 1987.
17. The ARIC Investigators. Atherosclerosis Risk in Communities (ARIC) Study Surveillance Component Procedures Protocol 3, Version 4. Chapel Hill, NC: Collaborative Studies Coordinating Center, University of North Carolina, 1987.
18. Barnard J, Meng XL. Applications of multiple imputation in medical studies: from AIDS to NHANES. *Stat Methods Med Res* 1999; 8:17–36.
19. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol* 2004;113:101–108.
20. Bisgaard H. Pathophysiology of the cysteinyl leukotrienes and effects of leukotriene receptor antagonists in asthma. *Allergy* 2001;56(suppl 66): 7–11.
21. Zhao L, Funk CD. Lipoxygenase pathways in atherogenesis. *Trends Cardiovasc Med* 2004;14:191–195.
22. Kramer PR, Kramer SF, Guan G. 17 Beta-estradiol regulates cytokine release through modulation of CD16 expression in monocytes and monocyte-derived macrophages. *Arthritis Rheum* 2004;50:1967–1975.
23. Xing D, Feng W, Miller AP, Weathington NM, Chen YF, Novak L, Blalock JE, Oparil S. Estrogen modulates TNF-α-induced inflammatory responses in rat aortic smooth muscle cells through estrogen receptor-beta activation. *Am J Physiol Heart Circ Physiol* 2007;292: H2607–H2612.
24. Miller AP, Feng W, Xing D, Weathington NM, Blalock JE, Chen YF, Oparil S. Estrogen modulates inflammatory mediator expression and neutrophil chemotaxis in injured arteries. *Circulation* 2004;110:1664–1669.
25. Zaitsu M, Narita S, Lambert KC, Grady JJ, Estes DM, Curran EM, Brooks EG, Watson CS, Goldblum RM, Midoro-Horiuti T. Estradiol activates mast cells via a non-genomic estrogen receptor-alpha and calcium influx. *Mol Immunol* 2007;44:1977–1985.
26. de Marco R, Locatelli F, Sunyer J, Burney P. Differences in incidence of reported asthma related to age in men and women. A retrospective analysis of the data of the European Respiratory Health Survey. *Am J Respir Crit Care Med* 2000;162:68–74.
27. Balzano G, Fuschillo S, Melillo G, Bonini S. Asthma and sex hormones. *Allergy* 2001;56:13–20.
28. Toren K, Brisman J, Jarvholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. *Chest* 1993; 104:600–608.
29. Chapman KR, Tashkin DP, Pye DJ. Gender bias in the diagnosis of COPD. *Chest* 2001;119:1691–1695.